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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,768	12/02/1998	JEFFRY D. WATKINS	P-IX-2947	4594

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/11/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/203,768	WATKINS ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *7-46* is/are withdrawn from consideration.

5)☒ Claim(s) *1-4,47 and 48* is/are allowed.

6)☒ Claim(s) *5, 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-48 are pending.

Claim 1 has been amended.

2. Claims 7-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

3. Claims 1-6 and 47-48 are under examination.

4. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 1-4 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to the claims.

Response to Arguments

7. The rejection of claim 5 under 35 U.S.C. 112, first paragraph, is maintained.

The response filed 12/31/02 has been carefully considured but is deemed not to be persuasive. The response states that the claim dos not recite and therefore is not limited to a method of in vivo administration for treatment of cancer and that the specification teaches administration to reduce proliferation and to detect neoplastic cells

and the response cites Walsh for teaching antibody based pharmaceuticals and some of them are directed to treatment of cancer (see pages 2- 5 of response).

In response to these arguments, as stated in the rejection the claim as written is drawn to pharmaceutical compositions which read on in vivo treatment for cancer. However, the data presented to support the enablement of the claim is based on cell culture, in vitro studies. While the specification at the recited pages (page 28 and 30) does disclose pharmaceutical compositions, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment of cancer. While Walsh teach antibodies to tumor antigens, the antigens have been well characterized and methods for with the antibodies to these antigens bind have been shown to be successful for treatment of cancer. This is in contrast to the antigen LH11238 which the claimed antibody binds to. The specification only discloses in vitro data of binding of the antibody to tumor cells and as evidenced from the references cited in the rejection the art does not recognize a clear correlation between in vitro data and in vivo data. The antigen to which the claimed antibody binds to has not been clearly demonstrated as a target for cancer therapy or whether targeting the antigen in vivo with an antibody would result in tumor killing or treatment. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed antibodies with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice

the claimed invention. Amending the claim to remove 'pharmaceutical" before composition would be sufficient to obviate this rejection.

The following is a NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

8. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human monoclonal antibody or antigen binding fragment thereof comprising three CDRs from SEQ ID NO:2 and three CDRs from SEQ ID NO:4 or a human monoclonal antibody or antigen binding fragment thereof having a conservative substitution in SEQ ID NO:2 and 4 wherein the antibody binds the same antigen as the monoclonal antibody comprising SEQ ID NO:2 and 4, does not reasonably provide enablement for any antibody or antigen binding fragment thereof having any conservative substitutions in SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds just any neoplastic cell or antigen thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any antibody with any conservative substitutions in SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds to any neoplastic cell or antigen thereof.

The specification teaches an antibody comprising SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds the LH11238 antigen. The specification teaches conservative substitutions in the antibody such that the antibody maintains its function of selectively binding a tumor specific antigen (see page 8, lines 11-16) which means in this instance the LH11238 antigen. The specification does not enable any antibody with conservative substitutions that binds to just any neoplastic cell or any antigen thereof.

The claims encompass any antibody with any conservative changes in the CDRs in SEQ ID NO:2 and SEQ ID NO:4 wherein the antibody binds any neoplastic cell or antigen. The claims are not commensurate in scope with the enablement provided in the specification. The claims encompass any conservative changes in the antibody wherein it is known in the art that changes in amino acid sequences have a profound effect on function. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, PTO 892, Attach to No11). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims

which may contain any conservative substitution in the CDRs, have the required binding function to the same antigen as that which the antibody having SEQ ID NO:2 and 4 binds. In addition, Colman (Research in Immunology 145:33-36, 1994, PTO-892, paper #24) teach that "The above examples paint a confusing picture of the specificity of antibody-antigen interaction. In one structural context, a very conservative substitution may abolish binding; in another, a nonconservative substitution may have very little effect on the binding" (see page 35, left column). Thus, while it may be true that one can make an antibody with conservative substitutions in the CDRs, it would require undue experimentation to predict which substitutions would produce an antibody that would retain binding to just any neoplastic cell or antigen thereof except the same antigen as that bound by the antibody of SEQ ID NO:2 and 4. In other words the claims broadly read on changing the amino acid sequence of the CDRs of SEQ ID NO:2 and 4 such that it can bind any neoplastic cell or antigen thereof, however, the specification does not enable such changes that result in the antibody binding to just any neoplastic cell or antigen.

Therefore, undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Conclusions

9. Claims 1-4, 47-48 are in condition for allowance.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879